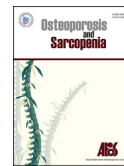


Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

Osteoporosis and Sarcopenia 2 (2016) 208–213

<http://www.elsevier.com/locate/afos>

Review Article

## Recent nutritional trends of calcium and vitamin D in East Asia

Hiroaki Ohta <sup>a</sup>, Kazuhiro Uenishi <sup>b</sup>, Masataka Shiraki <sup>c,\*</sup><sup>a</sup> Department of Clinical Medical Research Center, International University of Health and Welfare, Women's Medical Center of Sanno Medical Center, 8-5-35, Akasaka, Minato-ku, Tokyo, 107-0052, Japan<sup>b</sup> Laboratory of Physiological Nutrition, Kagawa Nutrition University, 3-9-21, Chiyoda, Sakado, Saitama, 350-0288, Japan<sup>c</sup> Research Institute and Practice for Involutional Diseases, 1610-1, Meisei, Misato, Azumino City, Nagano, 399-8101, Japan

Received 14 July 2016; revised 8 August 2016; accepted 12 August 2016

Available online 14 September 2016

## Abstract

Calcium intake may play an important role on bone health. The recent national nutritional survey in Japan revealed the gradual decrease in calcium intake to around 480 mg/day. In addition, the patients with low level of vitamin D become too large in proportion. The present perspective proposes to increase calcium intake in Asian population.

© 2016 The Korean Society of Osteoporosis. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Calcium; Vitamin D; Bone; Fracture

## 1. Introduction

Osteoporotic fractures continue to be a major health problem worldwide. Among osteoporotic fractures, hip fracture is the most serious morbid state and the secular trend in the incidence of hip fracture has been stabilized in Western countries. However, the incidence of hip fracture is rising in Asian countries [1]. Although the estimated number of hip fractures is recently decreasing in women in their seventies and eighties in Japan, the annual number of hip fractures among all age groups is still increasing [2]. In addition, the prevalence of vertebral fractures in Asian people has been reported to be higher than that in Caucasians [3]. Therefore, efforts to reduce fracture incidence should be concentrated in Asian countries.

Sufficient calcium intake and adequate serum vitamin D level have been considered to be essential factors in maintaining optimal function of body organs and systems. However, recent reports from the national nutritional survey of Japan in 2013 [4]

raised concerns about calcium nutrition (Fig. 1). Furthermore, we have investigated the level of serum vitamin D (25(OH)D) in patients with osteoporosis [5] and in postmenopausal women [6]. Those results suggested that a considerable number of subjects had an insufficient serum 25(OH)D level.

The low calcium intake and low serum 25(OH)D level are undoubtedly associated with the desire for weight reduction and for avoidance of skin darkening. Because the low calcium intake was associated with low energy intake leading to reduction of body weight (Fig. 2), that may be a reflection of national promotion against metabolic syndrome. In addition, recent sales of cosmetics for sun protection have markedly increased, suggesting the desire for protection against skin darkening. However, the trends of low calcium intake and vitamin D insufficiency seen in recent years may have a potential risk for future fractures or frailty, especially in women. Therefore, the aim of the present study is to drive the revision of calcium and vitamin D nutritions in not only Japan, but also in East Asian countries.

## 2. History of calcium intake in Japan (Fig. 1)

Calcium intake from food in Japan increased from the end of World War II to the 1990s. The extremely low calcium

\* Corresponding author. Research Institute and Practice for Involutional Diseases, 1610-1, Meisei, Misato, Azumino City, Nagano, 399-8101, Japan

E-mail address: [ripid@bh.wakwak.com](mailto:ripid@bh.wakwak.com) (M. Shiraki).

Peer review under responsibility of The Korean Society of Osteoporosis.

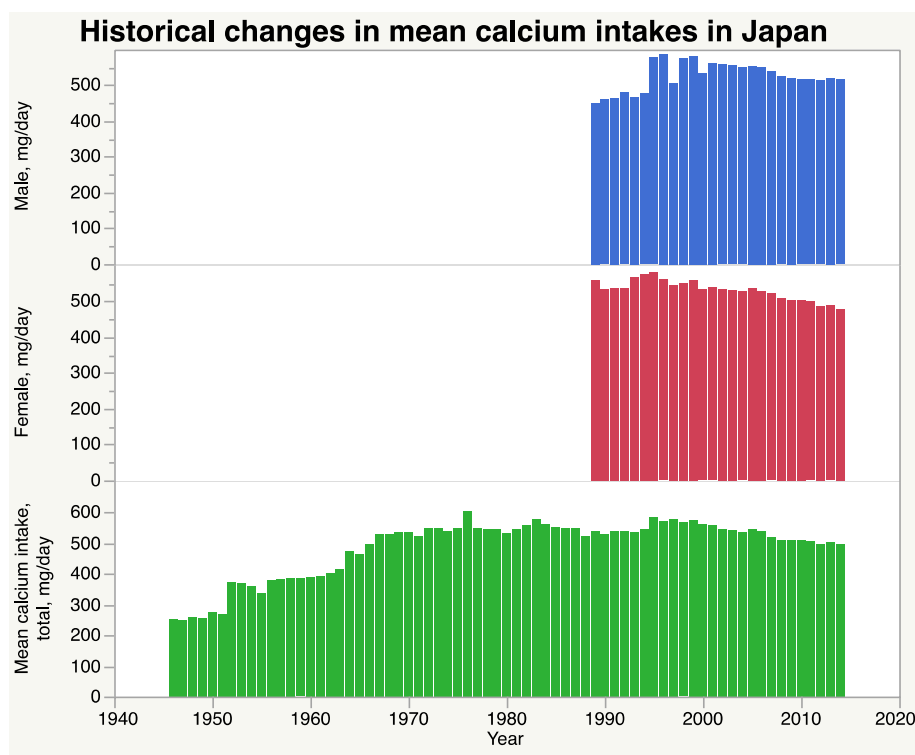


Fig. 1. The historical changes in calcium intake in Japan. The figure depicted the mean amounts of calcium intake in Japan after the finishing of World War 2nd. From 1946 to 1988, the mean values of calcium intake in total population (men and women) were reported, subsequently after 1989, the mean values of male and female were also reported in addition to that of the total population. The mean value of calcium intake in a total population was started around 250 mg/day at just after the War. That was subsequently increased dramatically to around 600 mg/day accompanying with economic boom at 1990ties. Then the calcium intakes of females were toward decrease in trend from 2007 when the national movement against metabolic syndrome had began. On the other hand, the decrease trend in calcium intake in males was not remarkable.

intake of 250 mg/day just after the war ended, was due to inadequate food supply and this turned to increase to approximately 600 mg/day during the post-war economic boom. In the subsequent era (2000~), recognized as an economic recession, the calcium intake reached to its nadir of approximately 550 mg/day. However, this trend ended at 2007 when national promotion against metabolic syndrome has been started and the national nutrition survey indicated the reduction in calcium intake to 500 mg/day or less in 2008, especially in women (Fig. 1) [4]. This trend was accompanied with a significant decline of body weight in women (Fig. 2), suggesting that the trend in decreasing calcium intake may be due to the women's desire to reduce their weight.

### 3. Calcium requirement in Asian people

Previously, we reported the calcium requirement in women by a calcium balance study [7]. The calcium requirements in young and old Japanese women were calculated as 543 and 788 mg/day, respectively. On the other hand, the recommended intakes of calcium for the young and old generations of women were 652 and 946 mg/day, respectively. Therefore, the calcium intake never exceeded the levels of calcium requirement or recommendation until now.

Joo N-S et al. [8] reported that the mean calcium intake and serum 25(OH)D level were 485 mg/day and 48.1 nmol/L, respectively in Korean people who participated in the KNHANES. The authors concluded that a calcium intake of at least 668 mg/day and serum 25(OH)D level of at least 50 nmol/L may be needed to prevent secondary hyperparathyroidism [8]. This estimated calcium intake obtained from the Korean population is very close to our proposal for the recommended daily calcium intake in the young generation based on the calcium balance study. As the recent mean calcium intake in Japan was almost the same as that in Korean people, the calcium deficiency in both populations was approximately 200 mg/day. The traditional dietary habit in Asian countries may be one of the barriers to increase in calcium intake, and therefore, calcium supplementation may be required to improve the calcium imbalance. According to the data from NHANES 2009–2010, the US females aged over 60 year-old took 842 mg/day of calcium from foods and supplementation. Around 40% of calcium originated from milk and dairy products in the US [9]. On the other hand, Japanese women aged sixties took 525 mg/day of calcium from foods. Around 30% of calcium was taken from milk [4]. Therefore, Japanese women took less total amount of calcium and also less proportion of calcium from relatively high bioavailable source comparing to those in the US.

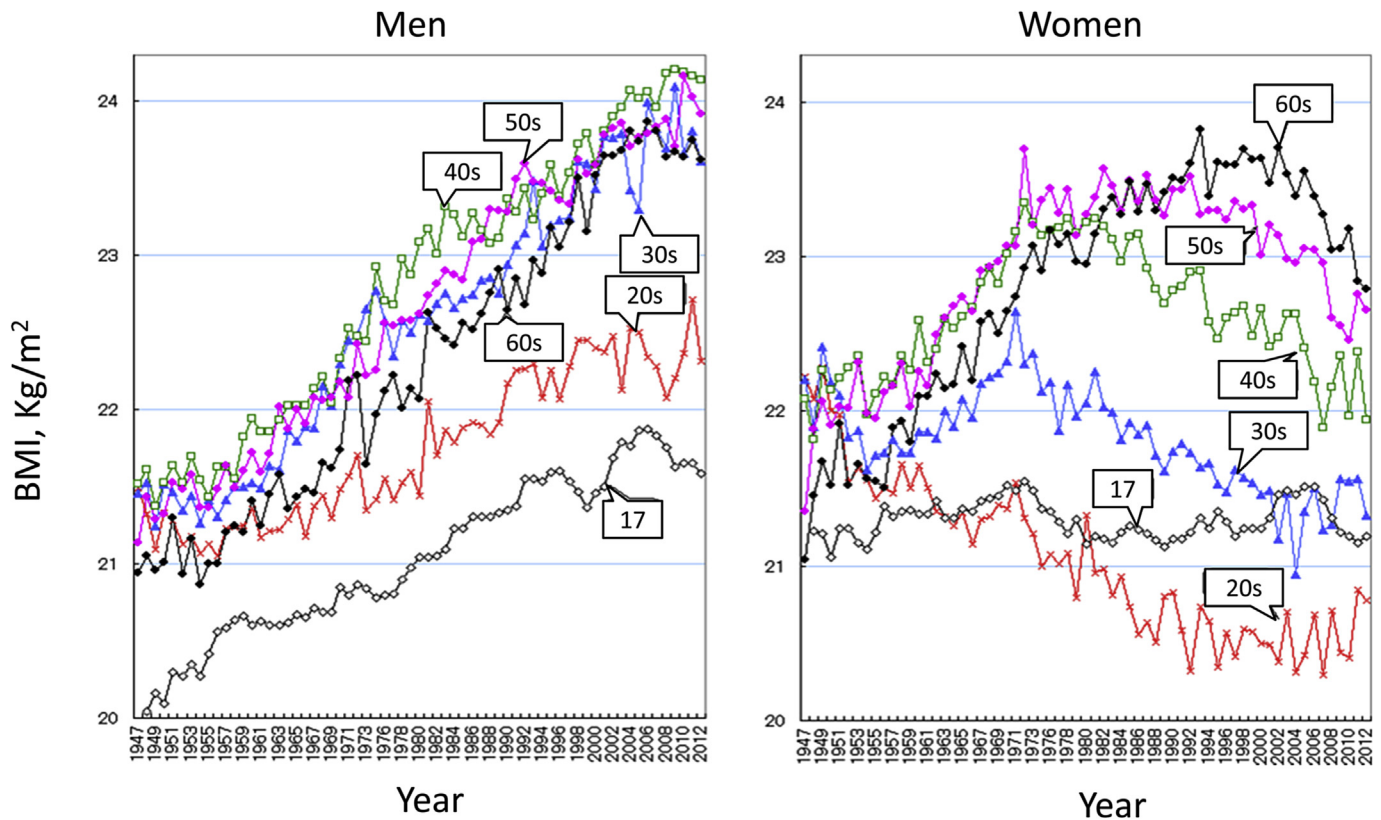


Fig. 2. The historical change in body size in Japanese men and women. The figure illustrated the change in body size of men and women divided by the age categories. The body size in men was steadily increased in every age categories. On the other hand, those in women were increased at once then turn down in almost of all age decades except for age 17 group. The timings towards down hill course were different in each age categories, namely age 20ies group led the trend firstly and the peak of BMI in each age group was delayed in accordance with advancing of age. Finally, the BMI of age 60ies peaked at 2000 and decreased thereafter. From 1960 and after, the BMI of age 20ies was below the mean at 1947. Data were obtained from [http://www0.nih.go.jp/eiken/chosa/kokumin\\_eiyou/index.html](http://www0.nih.go.jp/eiken/chosa/kokumin_eiyou/index.html), which was written in Japanese.

#### 4. Effects of calcium nutrition on PTH secretion and bone mineral density

As shown in the Korean population, calcium deficiency results in secondary hyperparathyroidism and low BMD. Calcium supplementation induced reduction in the levels of PTH and bone resorption markers [10]. Tai et al. reported that increased calcium intake by both dietary intake and supplementation increased BMD in meta-analysis [11]. Senior high school students were reported to have a lower calcium intake from food [12] and calcium or milk consumption is weakly correlated with BMD, suggesting that poor juvenile calcium nutrition may connect to inadequate formation of peak bone mass. The community-based nutrition education of calcium intake was effective to increase bone mass and reduced secondary hyperparathyroidism in postmenopausal Vietnamese women. In this prospective study, the postmenopausal women with low calcium intake (<400 mg/day) was educated to increase calcium intake to around 600 mg/day for 18 months. This study indicated that parathyroid hormone secretion was decreased by the increased calcium intake. The bone status measured by quantitative ultra-sound conduction in calcaneal bone was improved by the increase in calcium intake [13].

#### 5. Calcium intake from foods or supplementation on fracture prevention

Although the increase in calcium intake certainly connects to improve bone and calcium metabolism in women, there were many controversies regarding whether increase in calcium intake achieve the prevention of fractures or not. Two positive effects of high calcium intake on fracture prevention have been reported in a prospective cohort study and RCT [14,15]. One systematic review reported that higher dietary intake of calcium did not reduce the risk of fracture, but calcium supplementation significantly achieved the fracture risk reduction. However, the effects of calcium supplementation on fracture risk were weak and inconsistent [16]. The most recent prospective cohort study in Australia [14] reported that the highest quartile of calcium intake reduced the self-reported risk of fractures including hip, wrist and shoulder (OR for fracture was 0.75 (0.54–0.92 for 95% CI) after adjustment for confounding factors). The subgroup analysis revealed that the group with higher calcium intake of approximately 1000–1300 mg/day, resulted in various health benefits other than fracture prevention such as decrease in all causes of death, non-fatal cardiovascular disease and stroke [14].

The increase in calcium intake from food may have beneficial effects on bone in specified subpopulations having low calcium absorption from gut [14]. The ability of calcium absorption in the intestine was adapted to habitual calcium intake. Namely, active transcellular calcium transport in the duodenum is up-regulated by vitamin D-dependent processes in the subjects with low calcium intake [17]. On the other hand, calcium in people with high calcium intake was mainly absorbed in jejunum or ileum via passive transport [17].

A 12-year prospective cohort study evaluating the effects of calcium intake on fracture incidence did not support the hypothesis that higher consumption of milk or other food sources of calcium protects against fractures [18]. A total of 3 RCTs and one prospective observational cohort study examined the effects of calcium intake on fracture incidence. All these reports showed negative results, namely calcium supplementation did not reduce fractures [19–22]. However, those reports were mainly evaluating in Caucasian populations, where the calcium intake from food was estimated to be higher than that in the Asian population. In the Japan Public Health Centre-based Prospective Study [23], two different cohort studies evaluated the dairy calcium intake and observed 10-year incidence of self-reported vertebral fracture. The mean calcium intakes in the women of Cohorts I and II was 512 and 334 mg/day, respectively. The RR of vertebral fracture incidence in the lowest calcium intake (<350 mg/day) versus the highest group (>700 mg/day) was 2.10 (95% CI 1.25, 3.55). If the results obtained from Japanese study were extrapolated to entire Asian countries, the ideal daily calcium intake should be increased to around 700 mg/day. However, this target calcium intake might be hard to achieve because of the dietary customs in Asia. Therefore, a strategy to resolve fracture issues related to calcium insufficiency should focus on the reduction in the proportion of people who are taking extremely low calcium intake but not focused on the efforts to improve the mean calcium intake in entire population. For example, promoting another cup of milk or calcium tablet to increase another 200 mg/day of calcium in the people whose calcium intake of 400 mg/day or less on average. Further study is required to evaluate what level of calcium intake should be recommended in order to increase the minimum calcium intake or to change food customs leading to extreme calcium deficiency. Finally, the effects of increased calcium nutrition on bone health in the Asian population need to be further assessed. One limitation of the previous RCT using calcium supplementation on fracture prevention was the short observation period. Almost all studies observed the participants for less than 15 years. The calcium effects on bone may require a longer time to be concluded.

## 6. Calcium biology in other systems

Although calcium supplementation or increased intake of calcium had little effect on bone health, especially in Caucasian populations, other benefits of calcium intake for health problems have been reported. African Americans are known to have higher bone mass despite a lower calcium intake. The relative resistance of bone to secondary hyperparathyroidism

may be a cause of this black paradox [24]. However, African Americans have higher several other risks for chronic diseases such as cardiovascular diseases, stroke, obesity and insulin resistance syndrome [24] comparing to those in Caucasians. We have reported that calcium intake was negatively associated with the serum homocysteine level, which is a known factor to promote atherosclerosis [25]. Calcium supplementation or dairy product modulated lipid utilization and energy expenditure [26]. However, intervention studies using calcium supplementation or dairy products in obese women were controversial, namely one was positive [27] and the other was negative [28]. Dietary intake of calcium had been reported to correlate with hypertension [29]. The most recent meta-analysis revealed that the intake of dairy products might improve blood pressure and decrease in hypertension risk [30]. On the other hand, Bolland et al. reported the harm of calcium supplementation on cardiovascular events in healthy older women [31]. Thus, the health benefits of calcium intake or supplementation are currently controversial in Caucasian populations who took higher calcium intake comparing to Asian population.

## 7. Vitamin D nutrition and survival

Serum level of vitamin D is associated with increase in all cause of mortality in Asian population [32]. Although the exact mechanism(s) of vitamin D on mortality has not been fully elucidated, many association studies between vitamin D insufficiency and wide range of health related outcomes such as malignancies, cardiovascular diseases, autoimmune diseases, infections and metabolic diseases, had been carried out and the results indicated that vitamin D nutrition associated with those health related outcomes [33]. Vitamin D level also associated with fractures [6,34]. The attempts to reduce the fractures and other health problems related to vitamin D nutrition, have been carried out extensively. High-dose vitamin D supplementation (>800IU daily) was somewhat favorable in the prevention of hip fracture and any non-vertebral fracture in elderly people [35]. However, the other meta-analysis revealed that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes [36]. Those discrepancies may result in the differences in vitamin dose or in the subjects. In fact, Bischoff-Ferrari et al. reported that relatively high dose of vitamin D was shown to prevent fractures [35]. Murad et al. reported vitamin D use was associated with statistically significant reduction of falls (Odds 0.86: 95% CI 0.77–0.96) and the effect of vitamin D on fall was more prominent in the patients with vitamin D deficiency at baseline [37]. Therefore, we have to clarify what kind of subgroups will require pharmacological intervention with vitamin D.

In this context, we have to define the level of vitamin D deficiency. The reported definitions were varied from 50 nmol/L to 75 nmol/L. Those variations were due to the differences in outcomes. Because the level of PTH was taken for the evidence of vitamin D deficiency, the level of cut-off of serum 25(OH)D level was defined to 50 nmol/L [8,38]. On the other hand, when vitamin D related fracture occurrence was used as



an outcome of vitamin D deficiency, the cut-off value was 75 nmol/L [6]. The inverse relationship between serum 25(OH)D and PTH may be influenced by age, calcium intake, physical activity, renal function and even ethnicity [39]. Nakamura et al. reported that serum 25(OH)D levels less than 50 nmol/L indicated higher PTH level and that less than 70 nmol/L showed lower femoral neck BMD [40]. We have reported the significant relationship between serum 25(OH)D and incident non-vertebral fracture [6] and the cut-off value to reduce the incident long bone fractures was 62.5 nmol/L. Okazaki et al. demonstrated that the serum 25(OH)D level above which PTH reached a plateau was 70 nmol/L [41]. Dawson-Hughes proposed that the optimal levels of 25(OH)D were different to provide significant benefit to the segment of population [42]. Therefore, the uniform level of serum 25(OH)D could not be determined and it will be changed from 50 to 70 nmol/L depending on what type of outcome is expected.

## 8. Calcium and vitamin D interaction

It is well known that vitamin D resistance induces bone abnormalities such as large osteoid with lower mineralization, also known as osteomalacia or rickets. However, calcium infusion reversed bone and mineral abnormalities in a patient with vitamin D-resistant rickets [43]. In addition, bone phenotypes of VDR knock out mice were normalized by high calcium and phosphate dietary modifications [44]. Calcium absorption in the gut depends on two pathways: active transport via vitamin D action in the duodenum and the passive transport system in the jejunum and ileum [17]. Thus, the sufficient calcium supply may prevent the loss of vitamin D action via passive transport at ileum or jejunum [14,17]. Therefore, calcium intake is preferentially important to keep bone health.

## 9. Conclusion

In conclusion, Asian populations are evidently under calcium deficient. The mean calcium intakes in Japan and Korea were approximately 500 mg/day or less. This nutritional background is associated with secondary hyperparathyroidism, increased bone resorption and low bone mineral density. Although increased calcium intake from food or supplementation did not improve fracture incidence in Caucasian populations, fracture occurrence in Japanese women after the intervention of calcium nutrition had achieved to decrease in incident fracture. Thus, the calcium intake should be increased to 600 mg/day in populations with a low calcium level (<400 mg/day). When the calcium intake can be increased properly, it is expected that bone abnormalities of vitamin D deficiency may be compensated.

## Conflict of interest

The authors declare that we have no conflict of interest and the authors did not receive any support from the third party.

## References

- [1] Cooper C, Cole ZA, Hlroyd CR, Eari SC, Harvey NC, Dennison EM, et al., The IOF CSA Working Group on Fracture Epidemiology. Secular trends in incidence of hip and other osteoporotic fractures. *Osteoporos Int* 2011;22:1277–88.
- [2] Ohta H, Mouri M, Kuroda T, Nakamura T, Shiraki M, Orimo H. Decreased rate of hip fracture and consequent reduction in estimated medical costs in Japan. *J Bone Miner Metab* 2016. <http://dx.doi.org/10.1007/s00774-016-0760-0>.
- [3] Bow CH, Cheung E, Cheung CL, Xiao SM, Loong C, Soong C, et al. Ethnic difference of clinical vertebral fracture risk. *Osteoporos Int* 2012;23:879–85.
- [4] The national health and nutrition survey in Japan. 2014. <http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h26-houkoku.pdf>.
- [5] Ohta H, Uemura Z, Nakamura T, Fukunaga M, Ohashi Z, Hosoi T, et al., for the Adequate Treatment of Osteoporosis. Serum 25 hydroxyvitamin D level as an independent determinant of quality of life in osteoporosis with high risk of fracture. *Clin Ther* 2014;36:225–35.
- [6] Tanaka S, Kuroda T, Yamazaki Y, Shiraki Y, Yoshimura N, Shiraki M. Serum 25-hydroxyvitamin D below 25 ng/ml is a risk factor for long bone fracture comparable to bone mineral density in Japanese postmenopausal women. *J Bone Miner Metab* 2014;32:514–23.
- [7] Uenishi K, Ishida H, Kamei A, Shiraki M, Ezawa I, Goto S, et al. Calcium requirement estimated by balance study in elderly Japanese people. *Osteoporos Int* 2001;12:858–63.
- [8] Joo N-S, Hughes BD, Kim Y-S, Oh K, Yeum K-J. Impact of calcium and vitamin D insufficiencies on serum parathyroid hormone and bone mineral density: analysis of the fourth and fifth Korea National Health and Nutrition Examination Survey (KNHANES IV-3, 2009 and KNHANES V-1, 2010). *J Bone Miner Res* 2013;28:764–70.
- [9] Hoy MK, Goldman JD. Calcium intake of the US population. What we eat in America, NHANES 2009-2010. September 2014. Food Surveys Research Group Dietary Data Brief No. 13. [https://www.ars.usda.gov/ARSDUserFiles/80400530/pdf/DBrief/13\\_calcium\\_intake\\_0910.pdf](https://www.ars.usda.gov/ARSDUserFiles/80400530/pdf/DBrief/13_calcium_intake_0910.pdf).
- [10] Fardellone P, Brazier M, Kamel S, Gu  ris J, Graulet A-M, Li  nard J, et al. Biochemical effects of calcium supplementation in postmenopausal women: influence of dietary calcium intake. *Am J Clin Nutr* 1998;67:1273–8.
- [11] Tai V, Leung W, Grey A, Reid IR, Bolland MJ. Calcium intake and bone mineral density: systematic review and meta-analysis. *Br Med J* 2015; 351:h4183. <http://dx.doi.org/10.1136/bmj.h4183>.
- [12] Nakagi Y, Ito T, Hirooka K, Sugioka Y, Endo H, Saijo Y, et al. Association between lifestyle habits and bone mineral density in Japanese juveniles. *Environ Health Prev Med* 2010;15:222–8.
- [13] Hien VTT, Khan NC, Mai LB, Lam NT, Phuom TM, Nhung BT, et al. Effect of community-based nutrition education intervention on calcium intake and bone mass in postmenopausal Vietnamese women. *Public Health Ntr* 2009; 12:674–9. <http://dx.doi.org/10.1017/S1368980008002632>.
- [14] Khan B, Newson CA, Daly RM, English DR, Hodge AM, Giles GG, et al. Higher dietary calcium intakes are associated with reduced risks of fractures, cardiovascular events, and mortality: a prospective cohort study of older men and women. *J Bone Miner Res* 2015;30:1758–66.
- [15] Ensrud KE, Duong T, Cauley JA, Hearney RP, Wolf RL, Harris E, et al., for the study of osteoporotic fracture research group. Low fractional calcium absorption increases the risk for hip fracture in women with low calcium intake. *Ann Intern Med* 2000;132:345–53.
- [16] Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, et al. Calcium intake and risk of fracture: systematic review. *Br Med J* 2015; 351:h4580–4594.
- [17] Bronner F, Pansu D. Nutritional aspects of calcium absorption. *J Nutr* 1999;129:9–12.
- [18] Feskanech D, Willett WC, Stampfer MJ, Colditz GA. Milk, dietary calcium, and bone fractures in women: a 12-year prospective study. *Am J Public Health* 1997;87:992–7.
- [19] Warensj   E, Byberg L, Melhus H, G  deborg R, Mallmin H, Wolk A, et al. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *Br Med J* 2011;342:d1473–1482.

- [20] Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burkhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 2007;86:1780–90.
- [21] Salovaara K, Tuppurainen M, Kärkkäinen M, Rikkonen T, Sandini L, Sirola J, et al. Effect of vitamin D3 and calcium on fracture risk in 65- to 71-year-old women: a population-based 3 year randomized, controlled trial-The OSTPRE-FPS. *J Bone Miner Res* 2010;25:1487–95.
- [22] Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure. *Arch Intern Med* 2006;166:869–75.
- [23] Nakamura K, Kurahashi N, Ishihara J, Inoue M, Tsugane S, for the Japan Public Health Centre-based Prospective Study Group. Calcium intake and 10-year incidence of self-reported vertebral fractures in women and men: the Japan Public Health Centre-based prospective study. *Br J Nutr* 2009;191:285–94.
- [24] Heaney RP. Calcium-related chronic diseases in ethnic minorities: can daily consumption reduce health disparities? *J Nutr* 2006;136:1095–8.
- [25] Tanaka S, Uenishi, Yamazaki Y, Kuroda T, Shiraki M. Low calcium intake is associated with plasma homocysteine levels in postmenopausal women. *J Bone Miner Metab* 2014;32:317–23.
- [26] Zemel MB. Role of calcium and dairy products in energy partitioning and weight management. *Am J Clin Nutr* 2004;79(suppl. 1). 97S–12S.
- [27] Teegarden D, White KM, Lyle RM, Zemel MB, van Loan MD, Matkovic V, et al. Calcium and dairy product modulation of lipid utilization and energy expenditure. *Obesity* 2008;16:1566–72.
- [28] Yanovski JA, Parikh SJ, Yanoff LB, Denkinger BI, Calis KA, Reynolds JC, et al. Effects of calcium supplementation on body weight and adiposity in overweight and obese adults: a randomized clinical trial. *Ann Intern Med* 2009;150:821–9.
- [29] McCarron DA, Stanton J, Henry H, Morris C. Assessment of nutritional correlates of blood pressure. *Ann Intern Med* 1983;98:715–9.
- [30] McGrane MM, Essery E, Obbagy J, Lyon J, MacNeil P, Spahn J, et al. Dairy consumption, blood pressure, and risk of hypertension: an evidence-based review of recent literature. *Curr Cardiovasc Rep* 2011;5:287–98.
- [31] Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomized controlled trial. *Br Med J* 2008;336:262–6.
- [32] Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese post-menopausal women. *Bone* 2009;44:168–72.
- [33] Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JPA. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomized trials. *Br Med J* 2014;348:g2035–2054.
- [34] Cauley JA, Greendale GA, Ruppert K, Lian Y, Randolph Jr JF, Lo JC, et al. Serum 25 hydroxyvitamin D, bone mineral density and fracture risk across the menopause. *J Clin Endocrinol Metab* 2015;100:2046–54.
- [35] Bishoff-Ferrari H, Willett WC, Orav EJ, Lips P, Meunier PJ, Lyons RA, et al. A pooled analysis of vitamin D dose requirement for fracture prevention. *N Engl J Med* 2012;367:40–9.
- [36] Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. *Lancet Diabetes Endocrinol* 2014;2:307–20.
- [37] Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fatourehchi MM, et al. The effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:2997–3006.
- [38] Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. *J Clin Endocrinol Metab* 2011;96:E436–46.
- [39] Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the life-style: physiology and biomarkers. *Am J Clin Nutr* 2008;88:500S–6S.
- [40] Nakamura K, Tsugawa n, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, et al. Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogishi study. *Bone* 2008;42:271–7.
- [41] Okazaki R, Sugimoto T, Kaji H, Fuji Y, Shiraki M, Inoue D, et al. Vitamin D insufficiency defined by serum 25-hydroxyvitamin D and parathyroid hormone before and after oral vitamin D3 load in Japanese subjects. *J Bone Miner Metab* 2011;29:103–10.
- [42] Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *Am J Clin Nutr* 2008;88(suppl.):537S–40S. <http://ajcn.nutrition.org/content/88/2/537S.full.pdf+html>.
- [43] Balsan S, Garabédian M, Larchet M, Goraski A-M, Cournot G, Tau C, et al. Long-term nocturnal calcium infusions can cure rickets and promote normal mineralization in hereditary resistance to 1,25-dihydroxyvitamin D. *J Clin Invest* 1986;77:1661–7.
- [44] Amling M, Oriemel M, Holzmann T, Chapin K, Rueger JM, Baron R, et al. Rescue of the skeletal phenotype of vitamin D receptor-ablated mice in the setting of normal mineral iron homeostasis: formal histomorphometric and biochemical analyses. *Endocrinology* 1999;140:4982–7.